First-in-Class
α6GABA$_A$-Selective Modulators for Migraine and Other disorders

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FWF Der Wissenschaftsfonds.

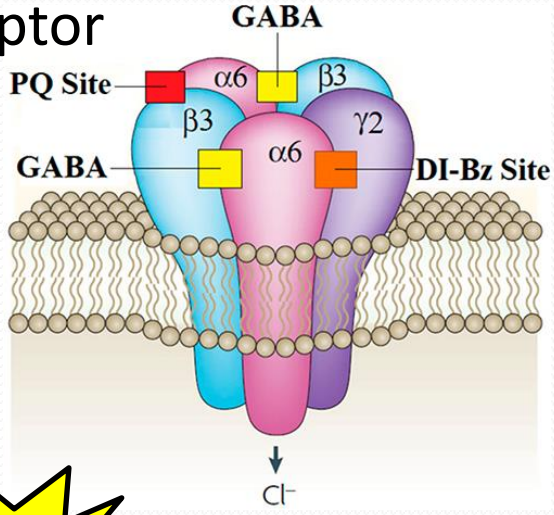
NIH National Institute of Neurological Disorders and Stroke

NIH National Institute of Mental Health

MOST 科技部 Ministry of Science and Technology

First-in-Class α6GABA$_A$R-selective PAMs

- α6GABA$_A$R: α6 subunit-containing GABA$_A$ receptor
- PAM: Positive allosteric modulator



α6GABA$_A$R-selective PAMs (Knutson et al., 2018)

- Different site of action as benzodiazepines
- Limited distribution of α6GABA$_A$Rs
  - CNS (Cerebellum)
  - Periphery (**Trigeminal ganglion**)

Safe

- **Effective in Migraine and other neuropsychiatric disorders**

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α6-Containing $GABA_A$ Receptors: Functional Roles and Therapeutic Potentials

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Clinical implications of α6GABA$_A$R PAMs

- Angelman syndrome
- Down's syndrome
- Essential tremor
- Tic disorders
- ADHD
- Obsessive Compulsive disorder
- Huntington's disease
- Schizophrenia
- Stress-associated disorders
- Anxiety disorders
- Depression/Bipolar disorder
- Autism spectrum disorder
- Alcohol use disorder
- Trigeminal-related pain
- Migraine

Table 2 in Sieghart et al. (2022) Pharmacological Review

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Proof of concept studies

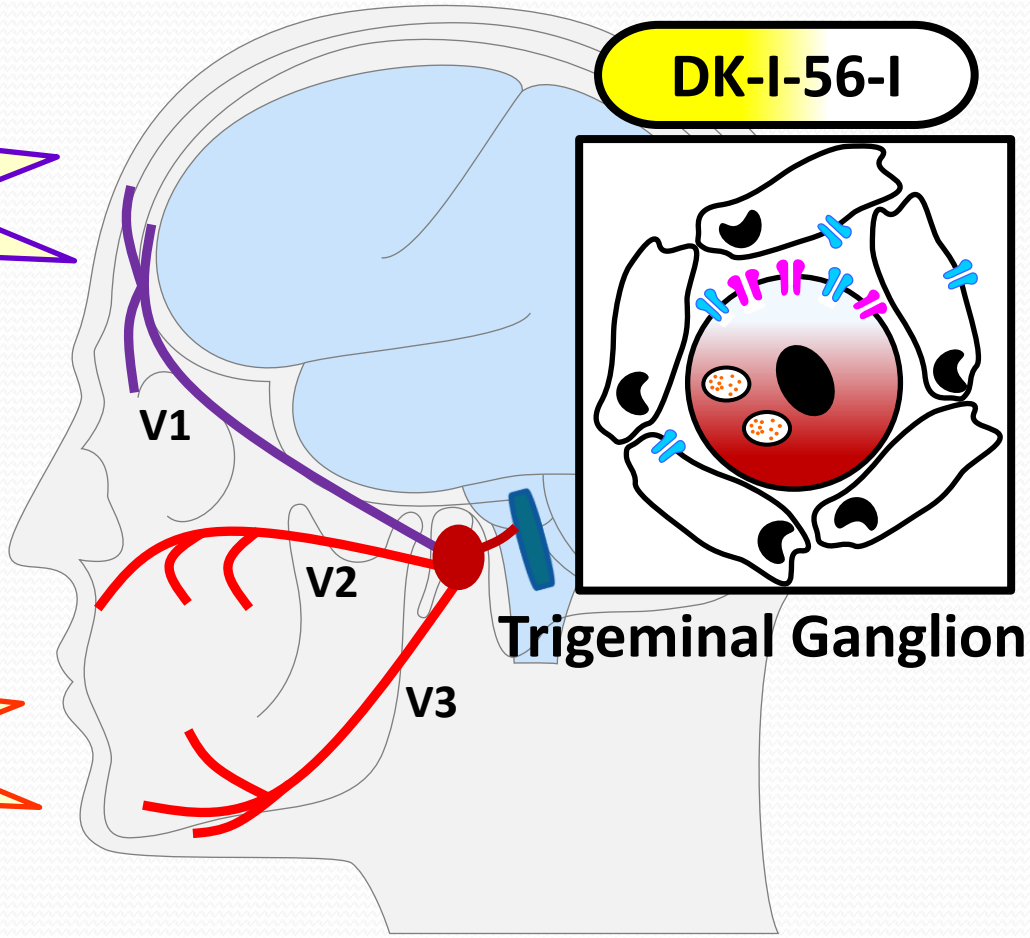
- Schizophrenia (Chiou et al., 2018; Lee et al., 2022)
- Tic disorders (Tourette syndrome) (Cadeddu et al. 2021; Wu et al., 2016)
- Essential tremor (Huang et al., 2022)
- Migraine (Fan et al., 2018; Tzeng et al., 2021; Chou et al., 2022)
- Trigeminal ganglia-related oral facial pain
  - Oral neuropathic pain (Vasović et al., 2019)
  - Dental pup injury (Yeh et al., 2021)
- More……. (Saint Cassia et al., 2022; Huang et al., 2022; Hung et al., 2022)

Migraine

Potential Indications of α6GABA$_A$R PAM

Migraine

Orofacial Pain



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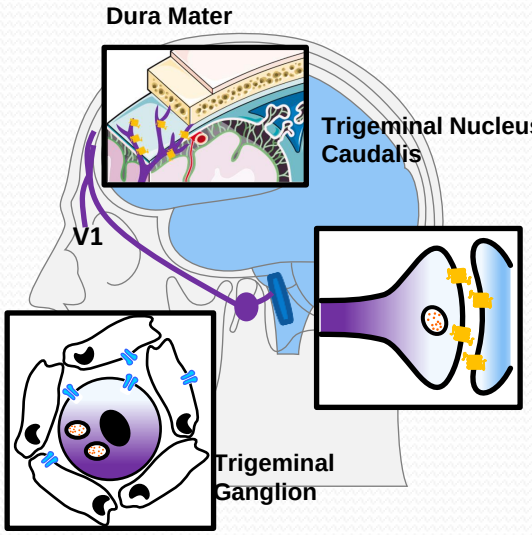
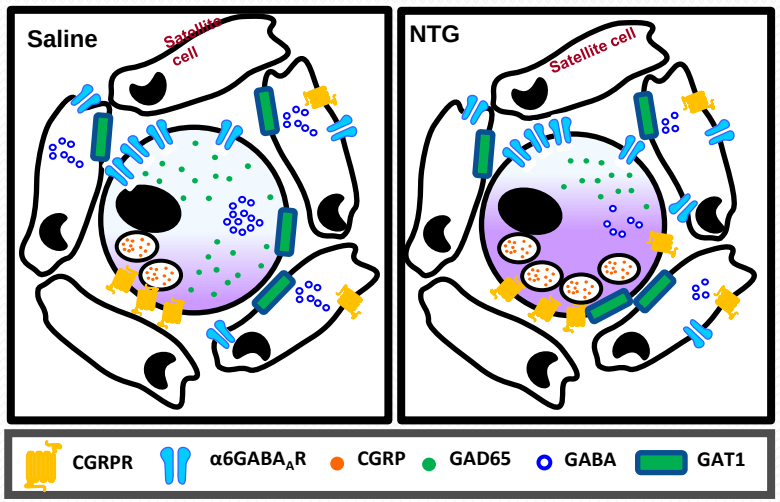
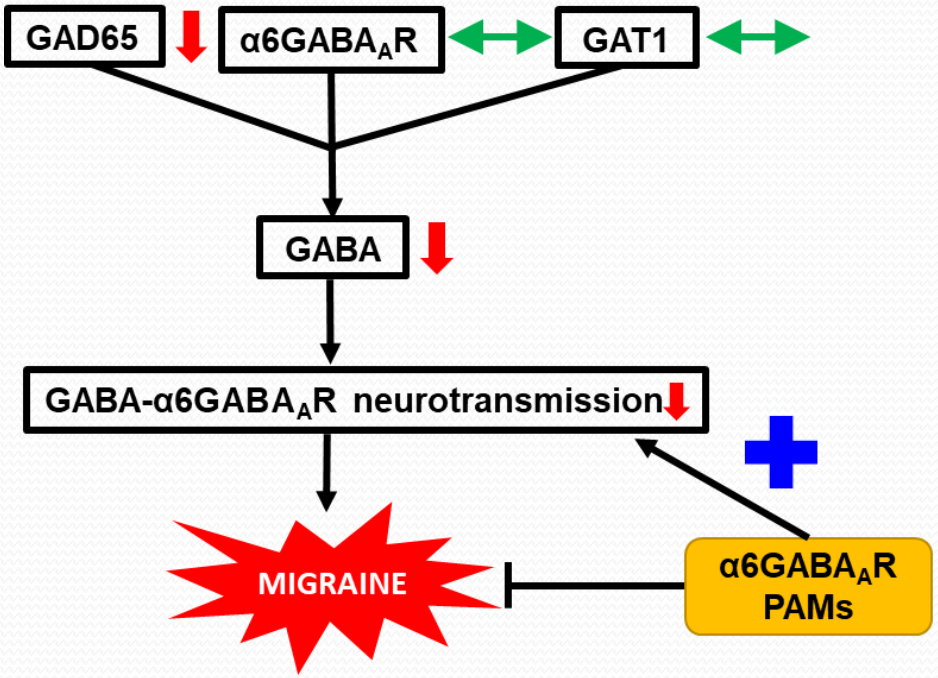
(A)


Dura Mater
Trigeminal Nucleus Caudalis
V1
Trigeminal Ganglion

(B)


Trigeminal Ganglion
Saline
Satellite cell
NTG
Satellite cell
CGRPR
α6GABA$_A$R
CGRP
GAD65
GABA
GAT1

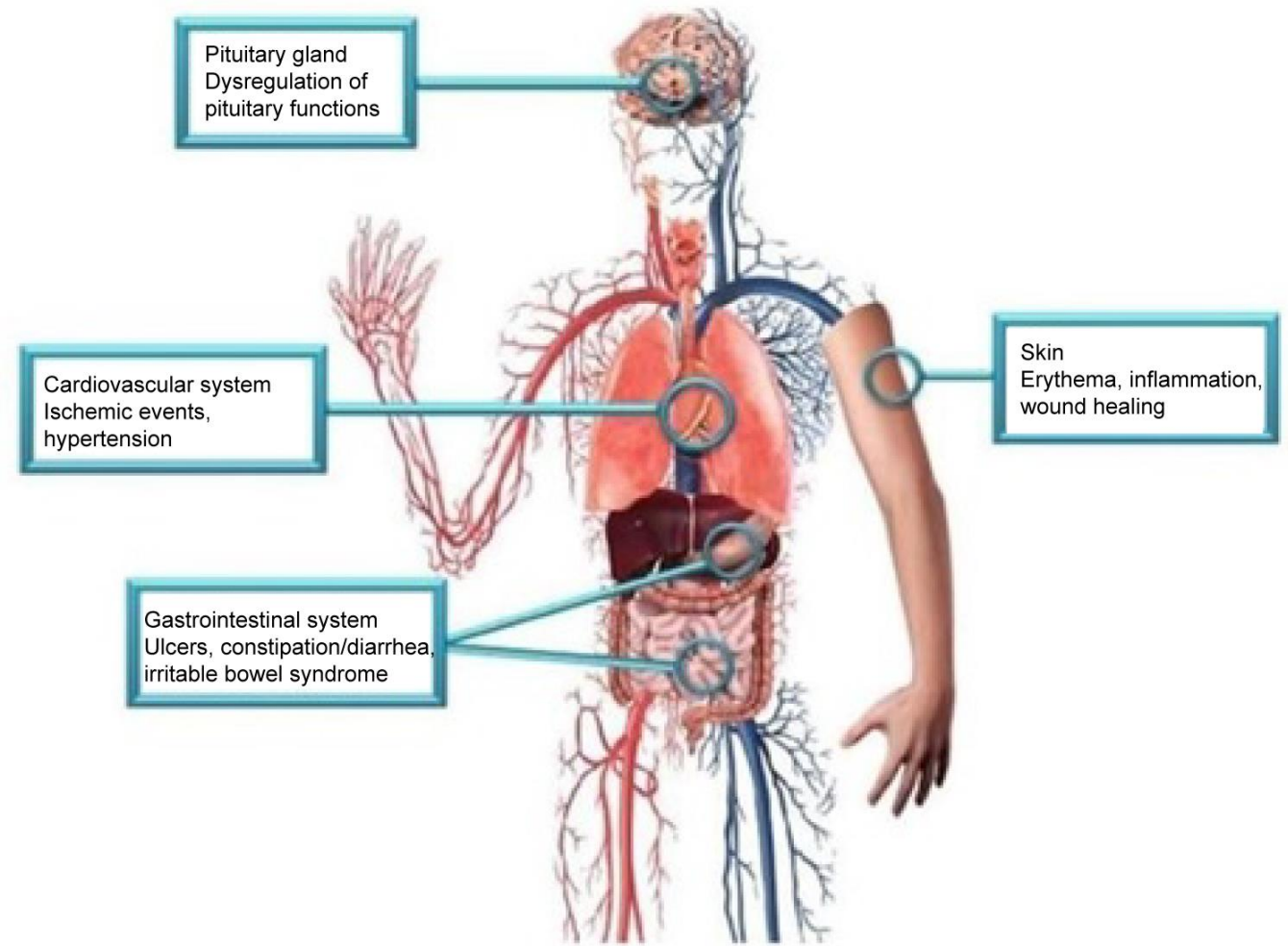
(C)


GAD65
α6GABA$_A$R
GAT1
GABA
GABA-α6GABA$_A$R neurotransmission
MIGRAINE
α6GABA$_A$R PAMs

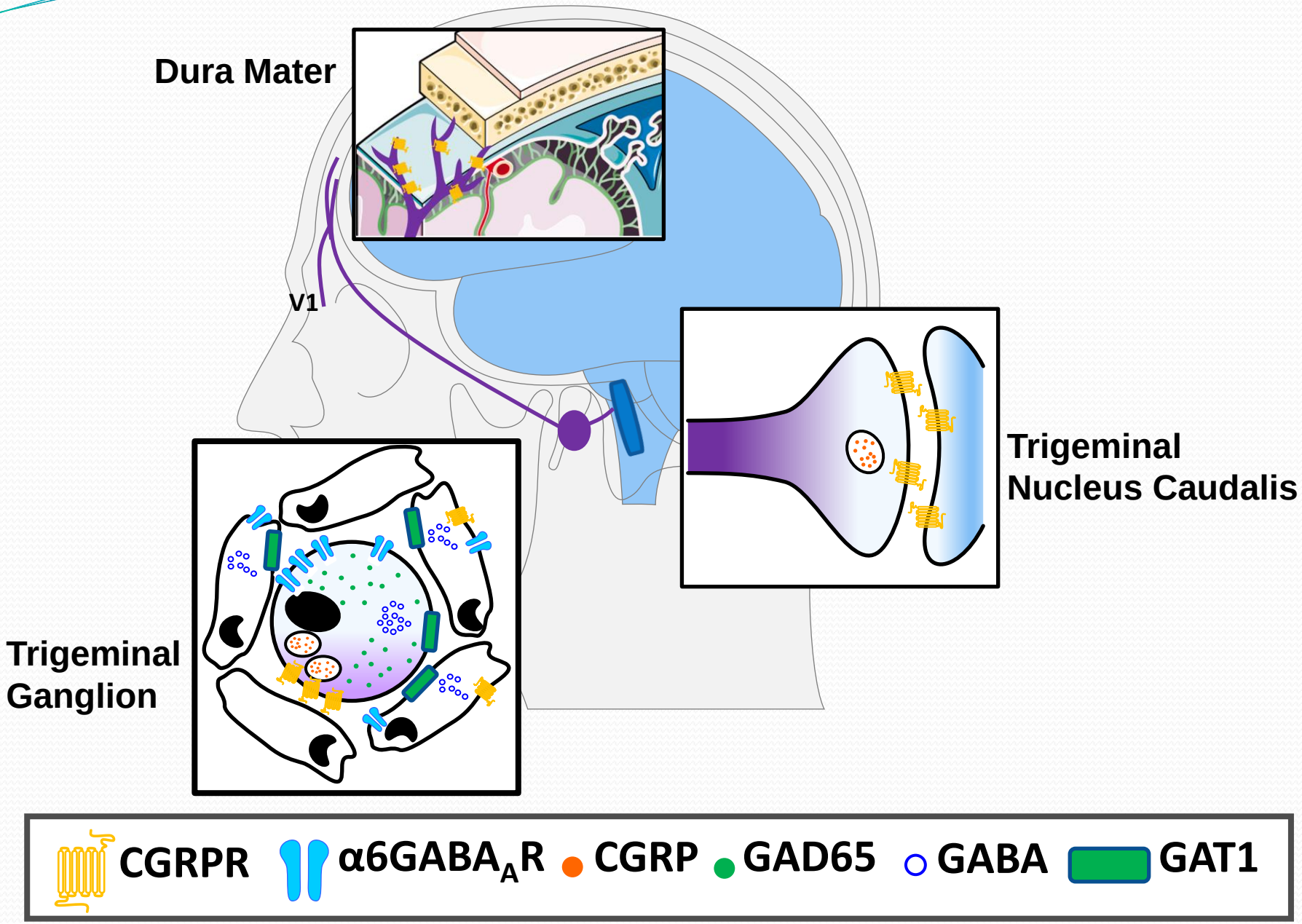
CGRP blocking antimigraine agents

Medication	Therapy	Company	FDA Approval	Efficacy (The change form baseline in MMDs)	Adverse events
Erenumab	Prevention	Amgen & Novartis	5/17, 2018	-3.2~ -3.7 (70-140 mg) vs. -1.8 days	Infusion reaction and constipation
Fremanezumab	Prevention	Teva	9/14, 2018	-4.0~-3.9 (225-675 mg) vs. -2.6 days	Infusion reaction and constipation
Galcanezumab	Prevention	Eli Lilly	9/27, 2018	-4.8~-4.6 (120-240 mg) vs. -2.7 days	Infusion reaction and constipation
Eptinezumab	Prevention	Alder	2/21, 2020	-4.0, -3.9 , -4.3 (30,100,300 mg) vs. -3.2 days	URI and UTI
Rimegepant	Prevention /Abortion	Biohaven	2/27, 2020	−4·3 (75mg) vs −3·5 days	Nausea and UTI
Ubrogepant	Abortion	Allergan	12/23, 2019	19.2%-21.2% (50-100 mg) vs. 11.8% (% Responders without pain in 2 hrs)	Nausea and dizziness
Atogepant	Prevention	AbbVie	9/28, 2021	−3.7, −3.9, −4.2 (10, 30, 60 mg) vs. −2.5 days	Nausea and dizziness

Risks of CGRP blockade



M. Deen *et al.*, "Blocking CGRP in migraine patients – a review of pros and cons," *The Journal of Headache and Pain*, vol. 18, no. 1, Sep. 2017.


Dura Mater
V1
Trigeminal Nucleus Caudalis
Trigeminal Ganglion
CGRPR
α6GABA$_A$R
CGRP
GAD65
GABA
GAT1

Advantages of α6GABA$_A$R-selective PAMs

- **First-in-Class**
  - First ligands highly selective to α6GABA$_A$Rs (Knutson et al., 2018)
- **Effective**: Proof-of-concept in animal models
  - Migraine (Fan et al., 2018, Tzeng et al., 2021)
  - Orofacial Pain
    - Trigeminal neuropathic pain (Vasović et al., 2019)
    - Dental pulp injury (Yeh et al., 2021)
    - TMJ disorders (Puri et al., 2011)
- **Good PK profiles** (Knutson et al., 2018)
  - Good metabolic stability (in vitro), HLM $t_{1/2}$: ~9 hr.
  - Excellent bioavailability (oral)

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Advantages of α6GABA$_A$R-selective PAMs

- **Functionally selective:** silent at other αx-GABA$_A$Rs
  - No BDZ-like side effects
    - Sedation
    - Amnesia
    - Tolerance
    - Addiction
    - Muscle weakness

- **Safe**
  - No off-target (eg. hERK) affinity (PDSP, NIMH, Brian Roth)
  - No liver or kidney cytotoxicity.

PDSP: psychoactive Drug Screening Program

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Intellectual Property

- U.S. Patent 10,865,203
- US Patent 11,427,582
- US Patent pending
- EP Validated in GB, CH, DE, FR, 3325479